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**Title: Posterior reversible encephalopathy syndrome due to immunosuppressant after living-donor
lobar lung transplantation: Report of a case**

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Abstract (57 words)

Living-donor lobar lung transplantation was performed in a 10-year-old boy with bronchiolitis obliterans (BO) after bone marrow transplantation (BMT) for recurrent acute myeloid leukemia (AML). He developed posterior reversible encephalopathy syndrome (PRES) due to calcineurin inhibitor (CNI) postoperatively, which was recovered with suspension of CNI. PRES should be considered one of the important morbidity after lung transplantation.

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a relatively new clinico-radiological entity and one of important side effects of calcineurin inhibitor (CNI). Herein we report a case of PRES induced by CNI after living-donor lobar lung transplantation (LDLLT) in a 10-year-old boy with bronchiolitis obliterans (BO) after bone marrow transplantation (BMT).

Case Report

A 6-year-old boy was diagnosed with AML in 2005 and treated with chemotherapy. In May 2008, at the age of 9, he underwent BMT from an unrelated, HLA-identical and ABO-mismatched donor for recurrent AML. Tacrolimus was administered intravenously then orally after BMT and stopped in September, 2008, since no acute graft versus host diseases (GVHD) occurred. The blood trough concentration of tacrolimus after BMT was maintained in a range between 10.7 and 23.9 ng/mL. In February 2009, he was diagnosed as having BO, as a pulmonary manifestation of chronic GVHD after BMT. In March 2009, sixteen days after the initiation of low dose oral tacrolimus treatment (1.0 mg/day) for BO, he lost consciousness and developed convulsion, hypertension (178 mmHg in systolic pressure), and paralysis with respiratory arrest requiring mechanical ventilation. The laboratory test revealed the white blood cells count to be $8.5 \times 10^9 / l$ and serum level of C-reactive protein to be below 0.09 mg/dl and his body temperature to be $36.6^\circ C$ on the day of symptom onset. Magnetic resonance imaging (MRI) of the brain demonstrated multiple focal areas of hyperintensity on both T2-weighted and FLAIR (fluid attenuated inversion recovery) images, predominantly in the white and gray matter of the occipital and posterior parietal lobes (Fig 1A, B). He was diagnosed as having PRES due to tacrolimus neurotoxicity. The blood trough concentration of tacrolimus was 8.4 ng/mL at the onset of PRES. The administration of tacrolimus was stopped immediately, and the symptoms rapidly and completely disappeared. MRI abnormalities gradually improved. After improvement of PRES, cyclosporine was re-initiated in April 2009, to treat BO. Under treatment with cyclosporine and steroid, however, his respiratory condition worsened and

continuous oxygen inhalation was initiated in September 2009, at the age of 10 and 3 months. His respiratory status further deteriorated because of BO progression with respiratory *Pseudomonas Aeruginosa* infection.

The patient was transferred to Kyoto University Hospital in January 2010. On admission, his vital capacity was 0.72 L (39.6% predicted), FEV1 was 0.27L (16.3% predicted), and arterial blood gas demonstrated a pH of 7.40, PaO₂ of 87.0 mmHg, and PaCO₂ of 55.8 mmHg with 2L/min oxygen administered via nasal cannula. The blood trough concentration of cyclosporine on admission was 72 ng/ml and the systemic/diastolic blood pressure was 120/62 mmHg.

Cadaveric lung transplantation was not a realistic option because brain death was legally accepted only for those older than 15 years old in Japan at that time. His parents, mother, 43 years old, and father, 44 years old, offered to be lung donors.

In February 2010, he underwent living-donor lobar lung transplantation with a left lower lobe from his mother and a right lower lobe from his father. The surgical aspects of the donor lobectomy, donor backtable preservation technique, and recipient bilateral pneumonectomy and lobar implantation have been previously described by Starnes' group¹. The patient was completely weaned from the ventilator on postoperative day (POD) 3. After lung transplantation, immunosuppressive therapy consisted of oral cyclosporine (target trough level: 250 -350 ng/ml), mycophenolate mofetil and prednisolone.

On POD 12, he complained of visual disturbance and brain MRI on that day demonstrated multiple focal areas of hyperintensity in both T2-weighted and FLAIR images, predominantly in the white and gray matter of the occipital and parietal lobes (Fig. 1C, D). The systemic/diastolic blood pressure was 157/108 mmHg, and the blood trough concentration of cyclosporine on POD 9 and POD 12 (on set of PRES) was 569 and 382 ng/ml, respectively. The laboratory test revealed the white blood cells count to be 8.1×10^9 /l and serum level of C-reactive protein to be 1.7 mg/dl and his body temperature to be 37.3 °C on the day of symptom onset. He was diagnosed as having recurrent PRES due to cyclosporine this time. Therefore, cyclosporine administration was stopped and enalapril maleate (inhibitor of

angiotensin converting enzyme) was started to reduce blood pressure. For immunosuppression after lung transplantation, basiliximab was administered on POD 13 and 17, replacing cyclosporine.

Mycophenolate mofetil and prednisolone administration was continued with same dose as that at the onset of PRES. After withdrawal of cyclosporine, cyclosporine concentration gradually decreased, and his visual symptoms were completely resolved on POD 15, which was 3 days after diagnosis and the start of treatment for PRES. Cyclosporine was restarted on POD 20 at a low dose. The brain MRI on POD 55 demonstrated that the lesion was improving (Fig. 1E, F). He was discharged from the hospital on POD 75 and now 11 months postoperatively, he has returned to a normal life without oxygen inhalation and is able to perform daily activities without visual symptoms. Under careful observation after restarting the administration of cyclosporine, there have not been any recurrent episodes of PRES.

Discussion

PRES is a relatively new clinico-radiological entity first described as reversible posterior leukoencephalopathy syndrome in 1996.² Originally, it denoted a reversible predominantly posterior leukoencephalopathy in patients with renal insufficiency, hypertension or immunosuppression. Classic neuroimaging in such patients shows edema involving the white matter in the posterior portions of the cerebral hemispheres, especially bilaterally in the parieto-occipital regions. The varieties of symptoms in PRES include headache, altered mentation, convulsion, unconsciousness, and visual disturbance.

Although the pathogenesis of PRES has not yet been sufficiently clarified, it is thought to involve vasogenic edema.³ When the systemic blood pressure increases above certain level, the autoregulation system that stabilizes brain blood flow fails and hyperperfusion results in leakage of blood plasma into the interstitium in the brain. The development of PRES under treatment with CNI is also thought to correlate with endothelial cell injury by CNI. In addition, it is possible that CNI agent may induce

hypertension, which may result in PRES⁴. Thus, PRES is an important morbidity after transplantation and the administration of CNI as an immunosuppressant.

Treatment for PRES mainly consists of controlling hypertension and convulsion. If the patient is administered CNI, the CNI should be discontinued, then restarted at a lower dose after improvement of symptoms, or converted (e.g. from tacrolimus to cyclosporine, or from cyclosporine to tacrolimus). The prognosis of PRES is generally considered reversible and benign; however, prolonged seizures, hypertension, or both may result in permanent neurological deficit and cerebral infarction⁵. Thus, appropriate and early diagnosis and treatment of PRES is highly critical.

The present patient experienced two episodes of PRES after different treatments for different diseases. The first episode occurred sixteen days after the initiation of low dose tacrolimus treatment for BO. Before that, he had already received tacrolimus after BMT without any symptoms of PRES, and had shown a higher trough concentration of tacrolimus than that at PRES onset. The second episode occurred twelve days after lung transplantation. He had been on cyclosporine preoperatively to treat BO and postoperatively after lung transplantation, with a relatively higher trough concentration on the day of PRES onset. For immunosuppressive maintenance after withdrawal of cyclosporine after lung transplantation, we did not use methylprednisolone after development of PRES because methylprednisolone administration was considered to be one of risk factor in the development of PRES^{2,6}. In the present case, blood pressure was high at onset of each episode, but the blood concentration of CNI did not seem to play a major role in the development of PRES. We speculate that the development both the first and second episodes of the PRES in the present patient correlated with CNI and hypertension as well as the patient's circumstance. The first episode occurred after BMT with chronic GVHD, in which endothelial injury by several cytokines was likely to have occurred during engraftment of bone marrow graft. The second episode occurred during the acute phase after lung transplantation, in which cytokines were also likely to have been activated. Horbinski et al. reported a case of PRES after cardiac transplantation and demonstrated endothelial activation, selective intravascular and perivascular

T-cell trafficking, and VEGF expression in astrocytes, neurons, and the endothelium histologically in brain biopsy specimens obtained to rule out brain infection.⁷

PRES after thoracic transplantation was rarely reported⁷, but Bartynski et al. reported a institutional retrospective study of PRES after solid organ transplantation. In their study, PRES developed in 21 (0.49%) of 4,222 patients who underwent solid organ transplantation, and 3 (0.64%) of 468 lung transplantation recipients developed PRES.⁸

In conclusion, we demonstrated PRES due to the neurotoxicity of different CNI developed twice in one patient. Both clinical symptoms and MRI findings were reversible and treatable with early diagnosis and immediate treatment including discontinuation or conversion of CNI. PRES should be considered in patients showing loss of consciousness, convulsion, or visual disturbance accompanied by hypertension after organ transplantation.

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Figure Legend

Figure 1.

Axial MRI FLAIR images of the present patient at onset of PRES in March 2009 during treatment of BO with tacrolimus (A, B), and in February 2010, POD 13 after lung transplantation with cyclosporine administration (C, D). Patchy areas of high signal intensity (arrows) were demonstrated in the bilateral occipital, parietal and temporal lobes. On FLAIR images (E, F) obtained 6 weeks after PRES onset, the signal intensity was significantly diminished.

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Figure 1.

